Remarks

The Applicants have amended Claim 1 to include the subject matter of Claims 3 and 4. Claims 3 and 4 have accordingly been cancelled. Claim 5 has been amended to account for the cancellation of Claim 4.

The Applicants also added new Claims 17 and 18 which are directed to types of liquid and solid dosage forms. Support may be found throughout the Applicants' Specification such as on page 5 in the last full paragraph, for example. Entry into the official file and consideration of the merits is respectfully requested.

Claims 1-5, 12-14 and 16 stand rejected under 35 USC §103 over the hypothetical combination of Habon with Xu 2001. The Applicants respectfully submit that one skilled in the art would not make the hypothetical combination as set forth in the rejection for the reasons below.

Claim 1 recites an inclusion complex comprising butylphthalide and cyclodextrin or cyclodextrin derivatives, wherein the cyclodextrin is selected from the group consisting of α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin, the cyclodextrin derivatives are selected from the group consisting of hydroxyethyl-β-cyclodextrin, hydroxypropyl-β-cyclodextrin, dihydroxypropyl-β-cyclodextrin, methyl-β-cyclodextrin, glucose cyclodextrin, maltose cyclodextrin, meltotriose cyclodextrin, carboxymethyl cyclodextrin and sulfonylalkyl cyclodextrin, and the molar ratio of butylphthalide to cyclodextrin or cyclodextrin derivatives is 1:1-10. It can be seen that the subject matter of Claim 1 is a product (i.e., an inclusion complex of butylphthalide) defined with its components and proportions thereof.

Xu 2001 relates to the therapeutic effects of butylphthalide. It neither discloses any dosage form of butylphthalide, nor discusses the possibility of preparing a dosage form of butylphthalide, nor mentions any properties of butylphthalide suitable for the manufacture of dosage form, especially an inclusion complex. In addition, there is no disclosure that any therapeutically active substance with any properties could be processed in a dosage form. Thus, those skilled in the art would not expect that butylphthalide would be suitable for preparation of all kinds of dosage forms, especially an inclusion complex. In addition, there is no disclosure that any therapeutically active substance with any properties could be processed in dosage form. Thus, those skilled in the art would not expect that butylphthalide would be suitable for preparation of all kinds of dosage forms, especially an inclusion complex with cyclodextrin or cyclodextrin derivatives based on Xu 2001.

Habon merely asserts that complexation with cyclodextrin decreases the hydrophobicity of poorly soluble drugs and results in enhanced dissolution rates and higher solubility, and simulates pharmacokinetic behavior of drug-cyclodextrin complexes in oral dosage forms only (see the abstract). However, Habon does not mention butylphthalide at all, nor provides any specific examples or evidence or sound theories to indicate that poorly soluble drugs with any other structures and/or properties would form complexes with any kind of cyclodextrins or cyclodextrin derivatives under any conditions. Therefore, those skilled in the art would not expect that all kinds of drugs could form complexes with cyclodextrin, and thus would not be motivated by Habon to form an inclusion complex of butylphthalide with cyclodextrin or cyclodextrin derivative as recited in Claim 1.

Inasmuch as both Xu 2001 and Habon are *silent* as to the ability of butylphthalide necessary for forming an inclusion complex of butylphthalide with cyclodextrin or cyclodextrin

derivative, they cannot provide a basis for obviousness. Thus, Xu 2001 and Habon fail to disclose or infer, at a minimum, any structure or property feature of butylphthalide for forming "an inclusion complex of butylphthalide with cyclodextrin or cyclodextrin derivatives," as recited in Claim 1. Thus, both disclosures are non-enabling as to how to produce the hypothetical inclusion complex.

The Applicants respectfully submit that prior art must be enabling for it to be employed in an obviousness rejection. In this case, the Applicants respectfully submit that both of Habon and Xu 2001 are non-enabling. The Habon disclosure is extremely limited and does not provide guidance to those skilled in the art as to how to form an inclusion complex of cyclodextrin with butylphthalide. It is not enough that Habon mentions forming complexes with cyclodextrin and it is not enough that Xu 2001 discloses butylphthalide. The combined disclosure must provide at least a minimum, "enabling" amount of disclosure that would guide those skilled in the art or teach those skilled in the art how to make the hypothesized composition. The Applicants respectfully submit that there is no such guidance and no teachings in the combined references. Thus, the Applicants respectfully submit that they are non-enabling and cannot support the rejection as set forth. Thus, the Applicants respectfully submit that the rejection should be withdrawn on this basis alone.

The rejection acknowledges that Xu 2001 does not explicitly teach the inclusion complex of butylphthalide with cyclodextrin or cyclodextrin derivatives. The rejection thus turns to Habon in an attempt to cure the deficiencies of Xu 2001. Thus, the rejection sets forth a motivational rationale not supported by the record, but rather based solely on the Examiner's belief of what one skilled in the art may have tried or recognized.

However, to set forth a rejection including Official Notice, the rejection must include some form of evidence in the record to support an assertion of common knowledge. If Official Notice is taken of a fact, unsupported by documentary evidence, then the basis for such reasoning must be set forth explicitly. The Examiner must provide specific factual findings predicted on sound technical and scientific reasoning to support the conclusion of common knowledge. *See* MPEP 2144.03(B).

It is well settled that "the Board [and the Examiner] cannot simply reach conclusions based on [their] own understanding or experience – on [their] assessment of what would be basic knowledge or common sense. Rather the Board [and the Examiner] must point to some concrete evidence in the record in support of these findings." *In re Zurko*, 258 F.3d 1379, 1386 (Fed. Cir. 2001). *See also, In re Lee,* 277 F.3d 1338, 1344-45 (Fed. Cir. 2002), in which the court required evidence for the determination of unpatentability by clarifying that the principles of "common knowledge" and "common sense" may only be applied to the analysis of evidence, rather than be a substitute for evidence.

Contrary to these requirements, the extant rejection provides no sound technical and scientific reasoning to support the above recited Official Notice. The relied upon action must be evidenced in the record, and cannot be based merely on speculation by the Examiner.

The position that it would have been obvious to one of ordinary skill in the art to substitute the technique of Habon in Xu 2001 is unsupported. Specifically, both Xu 2001 and Habon are *silent* regarding structure and/or property features of butylphthalide for forming an inclusion complex with cyclodextrin or cyclodextrin derivatives. Hence, there is not basis for alleging obviousness thereof. Further, Habon states that enhancement of bioavailability of drugs depends on the solubility of drugs, the solubility constant of the complexes, the molar ratio of

drug:cyclodextrin, etc. (see the abstract), and that when the dissociation equilibria are shifted toward the complex formation, the concentration of the absorbable free drug is lower and further decreases during the absorption processes due to the increasing cyclodextrin excess, so that the absorption rate of drugs can be accelerated or retarded (*see* page 832, left column, paragraph 3). Thus, Habon also acknowledges that complexation with cyclodextrin may not enhance bioavailability of a drug. In other words, one skilled in the art would not be motivated to use cyclodextrin to improve effects of poorly soluble drugs. Therefore, Habon cannot be relied upon to cure the deficiencies of Xu 2001.

As Xu 2001 and Habon do not disclose the same inclusion complex of butylphthalide with cyclodextrin or cyclodextrin derivatives as claimed, Xu 2001 and Habon do not render obvious the inclusion complex of butylphthalide with cyclodextrin or cyclodextrin derivatives as recited in Claim 1.

Obviousness can be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge readily available to one of ordinary skill in the art. *In re Kotzab,* 217 F.3d 1365, 1370 55 USPQ2d 1313, 1317 (Fed. Cir. 2000); *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). There is no suggestion in Xu 2001 and Habon to modify butylphthalide to form the inclusion complex of butylphthalide with cyclodextrin or cyclodextrin derivatives as recited in Claim 1, nor does common sense dictate the Examiner-asserted modification. The Examiner has not provided any evidence that there would be an obvious benefit in making the asserted modification of butylphthalide. *See KSR Int'l Co, v. Teleflex, Inc.,* 127 S. Ct. 1727, 82 USPQ2d 1385 (2007).

The only teaching of the inclusion complex of butylphthalide with cyclodextrin or cyclodextrin derivatives is found in the Applicants' disclosure. However, the teaching or suggestion to make a claimed combination and the reasonable expectation of success must not be based on an applicant's disclosure. *In re Vaeck*, 974 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Xu 1999 does not disclose the inclusion complex of butylphthalide with cyclodextrin or cyclodextrin derivative as claimed, and such inclusion complex cannot be expected based on Xu 1999 in combination with Habon either. Thus, Claims 15-16 involve inventive steps over Xu 1999 and Habon as well. The Applicants respectfully submit that the combined teachings of Xu 2001 and Habon simply provide no incentive for one skilled in the art to make the combination. The Habon disclosure is extremely short and does not provide the necessary motivation to make a hypothetical combination with Xu 2001, particularly in view of the lack of disclosure as to how such a combination should or could be made. Withdrawal of the rejection is respectfully requested.

Claims 6-11 stand rejected under 35 USC §103 over the hypothetical combination of Xu 2001 with Habon. The Applicants respectfully submit that this is merely reversal of the order of application of the two previously-discussed references. As such, they are also non-enabling on the one hand and, on the other hand, fail to provide the appropriate motivation for combination and reasonable expectation of success. Withdrawal of this rejection is also respectfully requested.

Claim 15 stands rejected under 35 USC §103 over the combination of Habon with Xu 1999.

As previously discussed, Habon is non-enabling since it provides utterly no guidance as to how a complexation with cyclodextrin and butylphthalide would or could be made. Thus, hypothetically combining Habon with Xu 1999 would result in the same non-enabling combined disclosure. Withdrawal of that rejection is also respectfully requested.

In light of the foregoing, the Applicants respectfully submit that the entire Application is now in condition for allowance, which is respectfully requested.

Respectfully submitted,

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